REMARKS

This Reply is responsive to the Final Office Action dated April 25, 2008 and the Advisory Action dated February 9, 2009. Pursuant to 37 CFR §1.116, this amendment cancels claims and places the application in better condition for appeal. No new issues have been raised and entry of the amendments and remarks submitted herein is respectfully requested.

I. Status of the Claims

Claims 68-174 were pending in this application and claims 68-106, 169 and 170 were withdrawn from consideration pursuant to a restriction requirement. Claims 107-168 and 171-174 were under examination at the time of the Final Office Action dated April 25, 2008 and the Advisory Action dated February 9, 2009. Claims 68-106, 115, 137, 141, 146, 148-156, and 168-171 are cancelled. Claims 107, 116, 138-140, 142-144, 147, 157, 162, 163, 167, 172, and 174 have been amended. Specifically, claim 107 has been amended to incorporate the limitation of previously pending claim 115, namely that the two or more different double stranded RNA sequences of the multitarget partially double stranded RNA molecule are separated by cleavage sequences. Claim 115 was under examination at the time of the Final Office Action dated April 25, 2008 and the Advisory Action dated February 9, 2009, and thus, this amendment raises no new issues. Claim 116 has been amended to depend from claim 107 and claims 138-140, 142-144, 147, 157, 163, 167, 172, and 174 have been amended to depend from claim 132. Claim 162 has been amended to correct a grammatical error. Applicants submit that no prohibited new matter has been introduced and these amendments narrow the issues for appeal. Upon entry of this amendment, claims 107-114, 116-136, 138-140, 142-145, 147, 157-167, and 172-174 will be

pending in the application. Reconsideration of the claimed subject matter is respectfully requested.

II. Rejection under 35 USC §103

Claims 107-168 and 171-174 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Werther *et al.* (US 5,929,040), Fire *et al.* (US 6,506,559), Heifetz *et al.* (WO 99/61631), Calabretta *et al.* (US 5,734,039) and Thompson *et al.* (US 6,146,886). The Examiner maintains her arguments that the invention is prima facie obvious because one of ordinary skill in the art would have a reasonable expectation of success by substituting the double-stranded RNA molecules disclosed in Fire *et al.* and Heifetz *et al.* into the multivalent antisense constructs dislcosed in Werther *et al.* and Calabretta *et al.* Despite the numerous papers cited showing the difficulty in obtaining gene specific silencing in vertebrate cells using double stranded RNA molecules as disclosed in Fire *et al.*, the Examiner maintains that the Applicants have simply reduced Fire's invention to practice for mammalian cells.

Without agreeing with the Examiner's rejection and in an effort to narrow the issues on appeal, claim 107 has been amended to specify that the two or more different double stranded sequences of the multitarget partially double stranded RNA molecule are separated by cleavage sequences. This subject matter was claimed in previously pending claim 115 and was under examination before the Examiner in the Final Office Action. Although the Examiner rejected claim 115 and related claim 146 (directed to an expression vector encoding a multitarget partially double stranded RNA molecule having two or more different double stranded sequences separated by cleavage sequences) on the

same grounds, she failed to establish a prima facie case based on the cited references for this embodiment of the invention. In fact, none of the references teach or suggest alone or in combination a multitarget partially double stranded RNA molecule comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target mammalian gene or mammalian pathogen gene, wherein said two or more different double stranded RNA sequences are separated by cleavage sequences.

Neither Fire *et al.* nor Heifetz *et al.* teach or suggest gene specific silencing in mammalian cells using double stranded RNA molecules let alone partially double stranded RNA molecules that can target multiple mammalian target sequences as claimed in the instant application. According to the Office Action, Werther *et al.* allegedly teaches a multivalent antisense molecule but does not disclose the use of double stranded RNA sequences or the expression of double stranded RNA sequences from a vector. Calabretta *et al.* allegedly describes a composition comprising two antisense molecules directed to one or more target genes and suggests that the antisense molecules might be expressed from a single vector using two different promoters. However, neither Calabretta *et al.* nor Werther *et al.* teach or suggest that the multivalent antisense sequences can be separated by cleavage sequences. Indeed, such an embodiment would not be necessary in the antisense constructs proposed by Calabretta *et al.* as each antisense sequence is transcribed from a separate promoter. Thus, none of the cited references teach or suggest separating double stranded RNA sequences comprised within a single multitarget partially double stranded RNA molecule with intervening cleavage sequences as claimed in the present invention. Thompson is relied upon for teaching

expression of therapeutic RNAs including ribozymes and antisense RNAs using a RNA pol III promoter. The disclosure in Thompson does not teach or suggest multitarget partially double stranded RNA molecules comprising cleavage sequences separating two or more different double stranded RNA sequences or vector constructs expressing such multitarget RNA molecules. In view of the above remarks, reconsideration and withdrawal of the rejection under §103(a) are respectfully requested.

CONCLUSION

Applicants believe that this Supplemental Reply adequately addresses all the rejections set forth in the Final Office Action dated April 25, 2008 and the Advisory Action dated February 9, 2009, and that the claims are now in condition for allowance.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Dated: March 27, 2009

Respectfully submitted,
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